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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IDENTIFICATION OF GENES INVOLVED IN ANGIOGENESIS, AND DEVELOPMENT OF AN ANGIOGENESIS DIAGNOSTIC CHIP TO IDENTIFY PATIENTS WITH IMPAIRED ANGIOGENESIS

(57) Abstract: The invention is directed to methods for angiotyping individual patients to predict the likelihood of whether a given individual will develop good vs. poor collaterals naturally. Accordingly, this can involve obtaining and providing a list of genes involved in collateral development. In particular, angiotyping individual patients can be used to predict the likelihood of whether a given individual will develop good vs. poor collaterals in response to specific angiogenesis therapy. From an array of genes that have been determined through experimental studies as being differentially expressed in tissues in which collaterals are developing in response to arterial occlusion, single nucleotide polymorphisms (SNPs), or other epigenetic changes, such as DNA methylation patterns, can be identified. SNPs and DNA methylation patterns are detected using microchips or similar technology assaying for all, or most, of the genes determined to play a role in collateral development. In addition, abnormally low or abnormally high differential expression of any combination of the candidate genes can be detected in such tissue as peripheral blood cells. The presence of a predisposition to develop poor vs. good collaterals is indicated by the presence of SNPs, and/or alterations in DNA methylation patterns, and/or difference in expression levels involving one or more of the genes.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38950

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68

US CL : 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 2003/0148334 A1 (SUN et al) 07 August 2003 (07.08.2003), abstract, Table 1.	1-4, 8-9
X	ZIMMER. R. et al. Expression Profiling and Interferon-beta Regulation of Liver Metastases in Colorectal Cancer Cells. Clinical and Experimental Metastasis. 2002. Vol 19, pages 541-550, see abstract, Fig. 2.	1-4, 8-9
X	LI, S. et al. Regression of Tumors by IFN- $\alpha$ Electroporation Gene Therapy and Analysis of the Reesponsible Genes by cDNA Array. Gene Thereapy. March 2002, Vol 9, pages 390-397, see abstract	1-4, 8-9

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38950

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-10, and 20-23, with regard to SPP1, MIG, and IP10

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

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### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-10 and 20-23, drawn to a method for predicting the likelihood that a subject will develop collaterals by assaying the expression of at least 3 genes.

Group 2, claim(s) 11-16, drawn to a method for predicting the likelihood that a subject will develop collaterals by assaying for a SNP or altered DNA methylation patterns in at least 3 genes.

Group 3, claim(s) 17-19, drawn to a kit comprising oligonucleotides for detecting genes from table 1.

Group 4, claim(s) 24-28, drawn to a method of promoting collateral formation by administering a composition that decreases expression of at least one gene in table 2 and/or increases expression of at least one gene in table 3.

The inventions listed as Groups 1-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature is deemed to be the involvement of genes in the development of collaterals. Claim 1, for example, is drawn to a method of assaying the expression level of at least 3 genes in a subject for the purpose of determining likelihood of developing collateral. Such assaying is taught by Zimmer and Thomas, Clinical & Experimental Metastasis, vol. 19, pages 541-550, 2002. Therefore, the claims do not relate to a single general inventive concept as they lack the same or corresponding special technical feature over the prior art.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

For Group 1, it is noted that claims which do not specify any genes from the tables will be searched according to the full scope of the claims. Therefore, the search for claims 1, 2, 8-10, and 20-23 will not be limited to any specific genes, however claim 2 will be limited to searching 3 genes. For claim 5-7, applicant is required to elect a specific combination of genes from the table. The first named species that will be searched with the generic claims will be IP10, MIG, and SPP1. Therefore, if applicant does not elect any additional groups, the generic claims will be searched to their full scope, claims 2-4 will be limited to any 3 genes, and claims 5-7 will be limited to searching IP10, MIG, and SPP1. With regard to claims 2-4, any additional combination of 5, 10, or 20 genes are considered to be a separate species and will require additional fees. Applicant may wish to elect more than one combination of genes, generically for claims 2-4, and specifically for claims 5-7. If so, it is noted that each combination will also be considered a separate species.

For group 2: for claim 13, applicant is required to elect a specific combination of genes from the table. It is noted that claims which do not specify any genes from the tables will be searched according to the full scope of the claims. Therefore, the search for claims 11, and 14-16 will not be limited to any specific genes, however claim 12 will be limited to searching 3 genes. Applicant is requested to indicate the combination of specific genes from table 1 which claim 13 will be limited to. If applicant wishes to further elect any additional combinations from claim 12, applicant may do so, however such is considered a separate species. Further, Applicant may wish to elect more than one specific combination of genes. If so, it is noted that each combination will be considered a separate species.

For Group 3: applicant is required to elect a specific combination of genes from table 1 to which the claimed oligonucleotides will be limited. Applicant may wish to elect more than one combination. If so, it is noted that each combination will be considered a separate species.

For Group 4: applicant is required to elect a specific combination of genes from tables 2 and/ or 3 to which the claims will be limited. Further, for claim 28, applicant is required to indicate a specific gene from table 3 for protein administration. Applicant may wish to elect more than one combination of genes for claims 24 and 28. If so, it is noted that each combination will be considered a separate species.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The genes listed in the various tables are

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drawn to structurally and functionally distinct products. These structurally and functionally different products lack the same or corresponding special technical feature.

### Continuation of B. FIELDS SEARCHED Item 3:

Caplus, medline, Genbank

search terms: angiogenesis, collateral, blood vessel, gene, nucleic acid, mRNA, RNA, expression, array, chip, SPP1, IP10, MIG, SCYB10, SCYB9